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REPORT

Patenting Risk Evaluation & Mitigation Strategies For Pharmaceuticals: A New Life Cycle Management Target for Patents?

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Under the Food and Drug Administration Amendments Act of 2007, the FDA can now require drug manufactures to submit a safety plan called ''Risk Evaluation and Mitigation Strategy'' (REMS). A recent publication indicates that 31 percent of new molecular entities and new therapeutic biologics include REMS.[1] Interestingly, a REMS may also be proprietary and associated with its own intellectual property rights, including patents. In the case of drugs, such patents can be listed in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (*Orange Book*), providing additional protection for a pharmaceutical product.[2] Even where the FDA does not require a formal REMS, an applicant for a new drug may develop a risk mitigation strategy to further enhance the safe use of the drug that is patentable and reflected in the labeling and associated information for its product approved by the FDA. This article explores the patenting of risk mitigation strategies for pharmaceutical products and identifies trends that may drive greater patenting in this area in the future.[3]

[1] The Pink Sheet, Vol. 70, No. 45, p. 25 (Nov. 10, 2008).

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1. What Is a REMS?

REMS are plans used to ensure that the benefits of a prescription drug outweigh that drugs risk of harm to the patient.[4] Prior to REMS, sponsors voluntarily created ''risk management plans'' or RiskMAPs to determine the risk of harm to patients. However, with the passage of the Food Drug Administration Amendments

[2] See, for example, U.S. Patent No. 7,141,018, which is listed in the *Orange Book* for thalidomide.

[3] There is an unanswered question about whether the 2007 FDA Amendments Act requires that the FDA make a REMS available to generic applicants and whether this law creates a conflict in the case where the FDA adopts a REMS that is already the subject of a patent. See ''Can a REMS Block a Generic?'', pp. 14-16, The Pink Sheet, Sept. 22, 2008. In this article we do not attempt to answer these questions, but instead address different types of risk mitigation strategies for pharmaceuticals that may be patentable subject matter under U.S. patent law.

[4] Masoudi, G.F. ''Legal Developments in the Enforcement of Food and Drug Law'' 63 *Food Drug L.J.* 585 at 586 (2008).

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Act of 2007 (FDAAA), the FDA can now require REMS.[5] Additionally, REMS can overlap with Accelerated Approval in terms of utilizing restricted distribution as an implementation tool.[6]

REMS is a defined set of steps carried out in the administration of a pharmaceutical product that reduces the risks of severe side effects.[7] A REMS can include a medication guide, patient package insert, a communication plan, elements to assure safe use, and an implementation system, and must include a timetable for assessment of the REMS.[8] The most restrictive elements of a REMS are the ''Elements to Assure Safe Use.'' This part of FDAAA describes many of the elements that sponsors previously addressed as ''restricted distribution plans.''[9]

The rationale behind REMS is to balance the potential harm a drug may cause with the possible benefit the drug may provide, and distribute the drug to the public as safely as possible. Thus, some pharmaceutical products that have significant side effects, may prompt the FDA to require a REMS before or after they are approved for marketing.[10] Therefore, the FDA can require manufacturers to submit a REMS either when the drug firms comes to market or when the FDA becomes aware of a new safety risk concerning the drug.

Finally, the statute contains a detailed and complex dispute resolution procedure related to REMS. Additionally, if a sponsor violates the terms of a REMS, then the drug may be misbranded, the sponsor may be fined, and the violation can open the sponsor up to civil penalties.[11]

2. Examples of REMS

Thalidomide is one example of a drug that has an FDA approved REMS. Thalidomide is a drug known to be effective for the treatment of both erythema nodosum leprosum and multiple myeloma.[12] However, thalidomide can also cause severe birth defects if taken during pregnancy.[13] Celgene Corporation (a distributor of thalidomide), created the ''System for Thalidomide Education and Prescribing Safety'' (STEPS®) program to help safely deliver Thalomid®[14] to patients. The STEPS® program was developed to minimize the chance of fetal exposure to Thalomid®. Importantly, Celgene also patented the managed delivery programs for products or drugs that are either teratogens or have other adverse effects that make them dangerous for certain patients.[15]

In contrast, Cephalon's Actiq is an example of a drug that needed a conversion from a RiskMAP to a REMS. Actiq is a predecessor to Fentora, which also denied approval by the FDA. Both Fentora and Actiq are used to treat chronic pain, but have the possibility to be abused. A practical consequence of the REMS requirement was a 2 percent drop in share price on Sept. 16, 2008.[16]

3. Patentability of Risk Mitigation Strategies

To fully appreciate the scope of potential patents that are possible, it is necessary to first understand how prescription pharmaceuticals are marketed and distributed, including the extent to which pharmacies rely upon computer systems when filling prescriptions. A prescription may be brought to the pharmacy by a patient, or transmitted telephonically or electronically directly to the pharmacy from the physician. When a patient picks up a prescription at the pharmacy, the pharmacist is required to call up pre-stored information about that patient before releasing the prescription. It is also possible for specific pharmaceutical products to trigger additional requests for data by the pharmacist at the time of filling the prescription, such as checking whether the patient is diabetic or has a heart condition.

The compilation and the availability of this kind of individual patient data that is either pre-stored on a pharmacy's computer system, or which is entered at the time of filling a prescription and triggered by the particular pharmaceutical product in question, lays the groundwork upon which a risk mitigation strategy may be carried out. For example, suppose a company has discovered that its drug for treating cancer has a certain risk of causing blindness that becomes unacceptably high when a patient is over a certain age and also has diabetes. Based on the company's research and discovery about the mechanism responsible for the side effect and its incidence in the different subpopulations, the company has created an algorithm for ensuring that its cancer drug will be administered so that the blindness side effect is reduced to a risk level that is acceptable given the benefit of the drug to the cancer patient in question. The algorithm utilizes the patient's age and diabetes status to calculate the risk of blindness. If the predicted risk of blindness falls below a certain medically acceptable level, then the prescription is authorized. This kind of method is patentable subject mat-

[5] Faden, L.B. and Milne, C. ''Pharmacovilgilance Activities in the United States, European Union and Japan: Harmonic Convergence or Convergent Evolution'' 63 *Food Drug L.J.* 683 at 687 (2008).

[6] See Faden note 5 above at 687.

[7] Complying with a REMS can potentially reduce the market penetration of a pharmaceutical product, but it will limit the occurrence of undesired side effects in the treated population. While a REMS may reduce sales of a pharmaceutical product, there may be a silver lining on the exclusivity side – namely, the possibility to patent the particular strategy developed by the drug applicant for mitigating the risk of side effects, thereby extending the exclusivity period.

[8] http://www.fda.gov/cder/regulatory/FDAAA/FR_QA.htm (visited October 19, 2008).

[9] See Masoudi note 4 above at 587.

[10] The FDA issued a Federal Register Notice dated March 27, 2008 indicating that 16 drugs (covering a total of 25 new drug applications, abbreviated new drug applications, and biologics license applications) needed approved REMS.

[11] See Masoudi note 4 above at 588.

[12] http://www.thalomid.com/thalomid_history.aspx (visited Oct. 16, 2008).

[13] *Id*.

[14] Thalomid® is the brand name for thalidomide.

[15] http://www.thalomid.com/steps_program.aspx (visited Oct. 16, 2008).

[16] Young, D. ''FDA Roundup FDA in a Cooperative Mood but Cephalon Not so Lucky'' 19 *Bioworld* 1541 (2008).

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ter[17] and provides a useful additional layer of protection for a pharmaceutical product.[18]

In the case of drugs, a patent strategy can be developed that lists the patent in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)*. Listing in the *Orange Book* is a critical benefit, and provides an additional layer of protection for a pharmaceutical product. This strategy uniquely implements the REMS framework to the patentee's advantage.[19] Thus, even where the FDA does not require a formal REMS, an applicant for a new drug may develop a risk mitigation strategy to further enhance the safe use of the drug that is patentable and reflected in the labeling and associated information for its product approved by the FDA.

4. Online Pharmacies and Implementation

Since about 2000, many pharmacies have begun operating on the Internet.[20] Online pharmacies offer a key implementation point for risk management. Data such as current prescriptions, previous medical history, sex, age, height, and weight can all be easily stored in an electronic database. These data can then be used to analyze the risk involved in use of the target drug. This type of personalized medicine helps maximize efficacy based on not only the patient's physical attributes, but his/her previous medical history and his/her current drug profile.

Additionally, ''verified'' online pharmacies have added benefits such as quality control and quality assurance. Programs such as the ''Verified Internet Pharmacy Practice Sites'' (VIPPS) created by the National Association of Boards of Pharmacy, help assure compliance with state licensing and inspection requirements. Furthermore, VIPPS compliance can help assure consumers of other important factors such as: (1) the patient's rights to privacy, (2) authentication and security of prescription orders, (3) adherence to a recognized quality assurance policy, and (4) meaningful consultation between patients and pharmacists.[21]

5. Conclusions

Many types of risk mitigation patents already exist for pharmaceuticals, biologics and medical devices. Personalized medicine represents an entire field aimed at maximizing efficacy based on an individual patient's genomic profile, enabling targeted administration of medical products to those individuals who will receive the greatest benefit from it. As genomic information, biomarker assays, and other types of clinical data collected from clinical trials continue to yield new insights into the mechanisms responsible for drug efficacy as well as drug side effects, the universe of potentially patentable risk mitigation strategies will continue to grow. Discovering such mechanisms and harnessing them through a computer-implemented risk mitigation strategy that controls whether a pharmacy can authorize the prescription to a particular patient will improve the lives of patients and provide valuable late-stage patents that aid in the life cycle management of pharmaceutical products.

Those charged with responsibility for patent life cycle management will have to coordinate proactively with regulatory and clinical personnel in order to identify these patenting opportunities. Many pharmaceutical patent attorneys are not familiar with drafting patent claims directed to computer-implemented methods, so effective protection of these inventions may require collaboration with computer patent attorneys to ensure that accurate terminology is used in the patent application.

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[17] Computer implemented methods are patentable provided they meet the requirements of 35 U.S.C. 101, 102, 103 and 112. In particular, although mathematical algorithms *per se* may not meet the utility requirement, *Gottschalk v. Benson*, 409 U.S. 63, 71-72, (1972), when they are implemented in a way that satisfies the machine or transformation test, then they are patentable subject matter under 35 U.S.C. 101. *In re Bilski*, __F.3d___(Fed. Cir. 2008)(en banc).

[18] For example, claim 1 of U.S. Patent No. 7,141,018, listed in the *Orange Book* for Thalomid, reads as follows:

A method for treating a patient having a disease or condition which is responsive to thalidomide while restricting access to thalidomide for patients for whom thalidomide may be contraindicated, the method comprising permitting prescriptions for thalidomide to be filled by a pharmacy only after the pharmacy has become aware of the generation of a prescription approval code for thalidomide for the patient from a computer readable storage medium, the generation of said prescription approval code comprising the following steps: a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for thalidomide; b. defining a set of information to be obtained from the patient, said set of information comprising the result of a determination of the ability of the patient to become pregnant and optionally comprising a determination that the patient is either (1) not currently pregnant or (2) currently pregnant; c. in response to said information set, assigning the patient to at least one of said risk groups and entering the patient, the information and the patient's risk group assignment into the medium; d. based upon the information and the risk group assignment, determining whether the risk that the adverse side effect is likely to occur is acceptable; and e. upon a determination that the risk is acceptable, generating the prescription approval code before the prescription is filled.

[19] See, for example, U.S. Patent No. 7,141,018, which is listed in the *Orange Book* for thalidomide.

[20] http://news.bbc.co.uk/2/hi/health/3572620.stm (visited October 23, 2008).

[21] http://vipps.nabp.net/verify.asp (visited October 23, 2008).